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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
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EXAMINER

18N2/1105

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ART UNIT	PAPER NUMBER
1812	28

DATE MAILED: 11/05/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 8/31/97.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1, 3-5, 8-16, 18-20, 23-32, 34 is/are pending in the application.

Of the above, claim(s) 4-5, 10-11, 14, 19-20, 25-26, 29, 34 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1, 3, 8-9, 12-13, 15-16, 18, 23-24, 27-28, 30-32 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims 1, 3-5, 8-16, 18-20, 23-32, 34 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

PTOL-326 (Rev. 10/95) ★ U.S. GPO: 199

DETAILED ACTION

Response to Amendment

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. The following rejections are withdrawn in light of Applicant's amendments: 1) The rejection of claims 13 and 28 under 35 USC 112, first paragraph; 2) the rejection of claims 13, 16, 18, 27-28, and 30 under 35 USC 112, second paragraph; 3) the rejection of claims 1, 3, 12, 15-16, 18, 27 and 30-32 under 35 USC 102(b) over Lowell et al.; and 4) the rejection of claims 13 and 28 under 35 USC 103 over Lowell et al.

Claim Objections

3. Claim 30 is objected to because of the following informalities: the first instance of "isolated" should be "isolating." Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. Claims 1, 8-9, 23-24, 27 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite for being in improper Markush format. Removal of "and" after C4 binding protein in the claim would overcome this objection.

However, but still applies

Claims 8-9 and 23-24 are indefinite with respect to the recitation in these claims of "structurally similar amino acids . . . (I, L,V), (F/V) . . . and combinations thereof." First, the

claims do not make clear how "structurally similar amino acids" are related to the recited groups of amino acids. Second, it is unclear whether "combinations thereof" refers to combinations of the structurally similar amino acids or to combinations of the various amino acid substitutions recited in the claim.

Claim 27 is indefinite with respect to the term "in phase," which is not an art-recognized term for a DNA encoding a fusion protein. This rejection could be overcome by amending "in phase" to "in reading frame," for instance.

Claim 32 is indefinite because it appears to recite that the host cell is transformed into the expression vector. This rejection could be overcome by amending the claim to recite " . . . which expression vector is capable, when transformed into the [expression vector] host cell, of expressing a DNA . . ."

Claim Rejections - 35 USC § 103

5. Claims 1, 3, 12-13, 15-16, 18, 27-28 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowell et al. in view of Fearon et al. (U.S. Pat. No. 5,256,642), Caras (WO 89/01041), Atkinson et al. (Immunology Today, 1987, 8, 212-215; Ref. 1-AT) and Bell et al. (U.S. Pat. No. 4,935,233).

Lowell teaches chimeric CR1/CR2 protein analogs including one in which the first two SCRs of CR2 are substituted for the first two SCRs of CR1 (CR2/CR1 XE) (see Fig. 1, p. 1936 and p. 1939). Lowell teaches a method to express the analog recombinantly which includes construction of DNA encoding the protein analog, transfection into host cells, and expression of

the analog (pp. 1933-1935). Lowell also discloses that cells expressing the chimeric protein were incubated with PBSA, which constitutes a pharmaceutical carrier (p. 1935). Although Lowell does not disclose that the chimeric protein CR2/CR1 XE binds either C3b or C4b, as recited in the claims, it was known in the prior art that the first two SCRs of CR1 are required for C4b binding while SCRs 8-9 (and possibly SCR 10) and SCRs 15-16 (and possibly SCR 17) constitute two C3b binding sites (see p. 5 of specification and Klickstein, 1988). Thus, CR2/CR1 XE would inherently bind C3b (via the CR1 SCRs) and bind C3dg and EBV (via the CR2 SCRs). Therefore, although Lowell does not disclose it explicitly, Lowell teaches a chimeric RCA protein analog which binds not only the ligand of the native protein from which it was derived, in this case C3b, but which also binds a ligand to which the native protein cannot bind, in this case C3dg and EBV. Lowell also teaches what was well known in the art at the time the invention was made that the RCA proteins are composed of SCR domains which are highly similar to one another (pp. 1931-1932). Lowell also teaches that each SCR is likely to interact only with adjacent SCRs, such that removal of SCRs not involved in ligand binding should not alter ligand binding, and further discloses that chimeric protein analogs comprising SCR domains from these genetically related proteins would be likely to result in functional chimeric proteins (pp.1942-1943). Lowell does not teach or suggest making a chimeric RCA protein analog other than CR1/CR2, as recited in the instant claims. However, Caras teaches that a soluble DAF can be used to inhibit complement activation *in vivo*, for the treatment of autoimmune and inflammatory diseases (p. 5), and Fearon teaches that a soluble CR1 can be used to inhibit inappropriate complement activation *in vivo*, for the

treatment of such disorders as inflammatory and autoimmune diseases (col. 25, lines 18-43). Both Fearon and Caras also teach that ligand-binding fragments of CR1 and DAF, respectively, can be used therapeutically (col. 24, lines 17-37 and p. 7). Furthermore, Atkinson teaches that all of CR1, DAF, MCP, C4bp and Factor H are critically important in regulation of complement activation (pp. 213-214). Thus, since Fearon and Caras teach that CR1 and DAF can be administered *in vivo* to inhibit autoimmune and inflammatory diseases and Atkinson teaches that CR1 and DAF, as well as the other RCA proteins, have interrelated effects in controlling the complement system, one having ordinary skill in the art would expect that administration of CR1 and DAF together would have additive effects in inhibiting inflammatory and autoimmune diseases. None of Fearon, Caras or Atkinson teach or suggest a chimeric protein containing both CR1 and DAF domains. However, Bell teaches chimeric proteins formed from covalently linked polypeptide cell modulators wherein the two modulators have different but complementary activity (col. 2, lines 3-29). Bell also discloses that a chimeric protein can be used to produce an enhanced effect than a single dosage form (col. 2, lines 32-36). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the chimeric CR1/CR2 protein taught by Lowell and substitute for the CR2 SCRs the SCRs of DAF, in order to produce a chimeric protein which would have C3b binding (via CR1) and DAF activity. Furthermore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the chimeric protein taught by Lowell and make an RCA analog in which the ligand-binding SCRs of DAF are linked to the entire soluble CR1, rather than

have substitution of the two N-terminal SCRs of CR2 for the two N-terminal SCRs of CR1, in order to obtain a chimeric RCA molecule which could bind C3b and C4b and have decay accelerating activity. One would be motivated to make this modification in order to obtain a molecule which could be used therapeutically to additively inhibit complement activation through binding of C3b and/or C4b, and through its decay accelerating activities as taught by Bell. One would be motivated to make either the full-length CR1/DAF chimeric protein or a CR1/DAF chimeric protein in which the first two SCRs of CR1 are missing because one would expect that administration of CR1 and DAF would have additive effects in inhibiting complement activation, and Bell teaches that administration of a chimeric protein will have the effect of the two single effectors administered separately. It also would have been obvious to one having ordinary skill in the art to make this chimeric protein using DNA encoding such a protein, expression vectors and host cells to recombinantly produce this protein, because Lowell used this method to make CR1/CR2 and because Bell teaches that chimeric proteins are preferably made by genetic engineering (col. 2, lines 37-44). Furthermore, one would have had a reasonable expectation of success because Lowell teaches that chimeric proteins containing the structurally and functionally similar SCR domains of CR2 were able to bind their native ligands in the CR2/CR1 chimera.

6. Applicant's arguments filed 31 July 1997 have been fully considered but they are not persuasive.

Applicant argues that since Lowell never looks at or predicts that one can alter functional activity in a chimeric protein, but rather discusses only the binding activity of the chimeric protein.

This argument is unpersuasive because the rejection that is instantly made is based not only upon Lowell but upon other references which would render the claimed invention obvious.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Brown whose telephone number is (703) 308-3668. The examiner can normally be reached on Mondays through Thursdays and on alternate Fridays from 8:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Stephen Walsh, can be reached on (703) 308-2957.

Official papers filed by fax should be directed to (703) 305-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**stephen.walsh@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive

information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

KEB
30 October 1997

Stephen Walsh
STEPHEN WALSH
SUPERVISORY PATENT EXAMINER
GROUP 1800